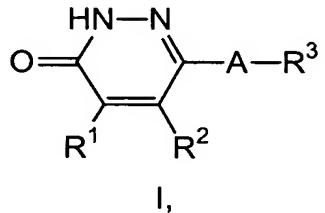


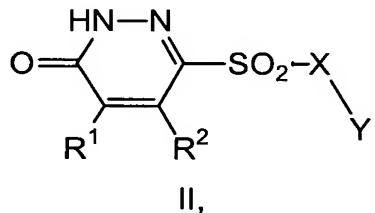
CLAIMS

1. A pharmaceutical composition comprising a first compound selected from:

5 a compound of formula I



and a compound of formula II



10 or a prodrug of said first compound, or a pharmaceutically acceptable salt of said first compound or said prodrug,

wherein:

A is S, SO or SO₂;

15 R¹ and R² are each independently hydrogen or methyl;

R³ is Het¹, -CHR⁴Het¹ or NR⁶R⁷;

R⁴ is hydrogen or (C₁-C₃)alkyl;

R⁶ is (C₁-C₆)alkyl, aryl or Het²;

R⁷ is Het³;

20 Het¹ is pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl, cinnolinyl, naphthyridinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyrimidopyridazinyl, pyrimidopyrimidyl, pyridopyrimidyl, pyridopyrazinyl, pyridopyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl,

25 oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, pyrrolopyridyl, furopyrindyl, thienopyridyl, imidazolopyridyl, oxazolopyridyl, thiazolopyridyl, pyrazolopyridyl, isoxazolopyridyl, isothiazolopyridyl, pyrrolopyrimidyl, furopyrimidyl, thienopyrimidyl,

imidazolopyrimidyl, oxazolopyrimidyl, thiazolopyrimidyl, pyrazolopyrimidyl, isoxazolopyrimidyl, isothiazolopyrimidyl, pyrrolopyrazinyl, furopyrazinyl, thienopyrazinyl, imidazolopyrazinyl, oxazolopyrazinyl, thiazolopyrazinyl, pyrazolopyrazinyl, isoxazolopyrazinyl, isothiazolopyrazinyl, pyrrolopyridazinyl,
5 furopyridazinyl, thienopyridazinyl, imidazolopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, pyrazolopyridazinyl, isoxazolopyridazinyl or isothiazolopyridazinyl; Het¹ is independently optionally substituted with up to a total of four substituents independently selected from R⁸, R⁹, R¹⁰ and R¹¹; wherein R⁸, R⁹, R¹⁰ and R¹¹ are each taken separately and are each
10 independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylenyloxycarbonyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹²R¹³, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido, phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl,
15 tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfenyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl,
20 pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to three substituents independently selected from hydroxy,
25 halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to two substituents independently selected from hydroxy, halo, C₁-C₄)alkyl, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C₁-C₄)alkyl-phenyl optionally substituted in the phenyl portion with one Cl, Br, OMe, Me or SO₂-phenyl wherein said SO₂-phenyl is optionally substituted in the phenyl portion with one Cl, Br, OMe, Me, (C₁-C₄)alkyl optionally substituted with up to five fluoro, or (C₁-C₄)alkoxy optionally substituted with up to three fluoro;
30

R^{12} and R^{13} are each independently hydrogen or (C_1-C_4)alkyl;

Het² and Het³ are each independently imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl,

- 5 benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy; Het² and Het³ are each independently optionally substituted with up to a total of four substituents independently selected from R^{14} , R^{15} , R^{16} and R^{17} , wherein R^{14} , R^{15} , R^{16} and R^{17} are each taken separately and are each independently halo, formyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylenyloxycarbonyl, (C_1-C_4)alkoxy-(C_1-C_4)alkyl, $C(OH)R^{18}R^{19}$, (C_1-C_4)alkylcarbonylamido, (C_3-C_7)cycloalkylcarbonylamido, phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl,
- 10 benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C_1-C_4)alkylsulfenyl, (C_1-C_4)alkylsulfonyl, (C_3-C_7)cycloalkyl, (C_1-C_4)alkyl optionally substituted with up to three fluoro or (C_1-C_4)alkoxy optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl,
- 15 thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R^{14} , R^{15} , R^{16} and R^{17} are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-(C_1-C_4)alkyl, (C_1-C_4)alkoxy-(C_1-C_4)alkyl, (C_1-C_4)alkyl optionally
- 20 substituted with up to five fluoro and (C_1-C_4)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R^{14} , R^{15} , R^{16} and R^{17} are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-(C_1-C_4)alkyl, (C_1-C_4)alkoxy-(C_1-C_4)alkyl, (C_1-C_4)alkyl optionally substituted with up to five fluoro and (C_1-C_4)alkoxy optionally substituted with up to three fluoro; and
- 25 R^{18} and R^{19} are each independently hydrogen or (C_1-C_4)alkyl;
- 30 X and Y together are $CH_2-CH(OH)-Ar$ or $CH_2-C(O)-Ar$, or

X is a covalent bond, NR^{20} or CHR^{21} , wherein, R^{20} is (C_1-C_3)alkyl or a phenyl that is optionally substituted with one or more substituents selected

from OH, F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³, and R²¹ is hydrogen or methyl, and

Y is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from Ar, OH, F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³;

Ar is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³;

n is independently for each occurrence 0, 1 or 2;

10 R²² is independently for each occurrence H, (C₁-C₆)alkyl, phenyl or naphthyl; and

R²³ is independently for each occurrence (C₁-C₆)alkyl, phenyl or naphthyl,

provided that when R³ is NR⁶R⁷, then A is SO₂; and

15 a second compound that is a cyclooxygenase-2 inhibitor, a prodrug of said second compound or a pharmaceutically acceptable salt of said second compound or said prodrug.

2. A composition of claim 1 wherein said first compound is a compound of formula I, wherein A is SO₂; R¹ and R² are each hydrogen; R³ is Het¹, wherein Het¹ is 5H-furo-[3,2c]pyridin-4-one-2-yl, furano[2,3b]pyridin-2-yl, thieno[2,3b]pyridin-2-yl, indol-2-yl, indol-3-yl, benzofuran-2-yl, benzothien-2-yl, imidazo[1,2a]pyridin-3-yl, pyrrol-1-yl, imidazol-1-yl, indazol-1-yl, tetrahydroquinol-1-yl or tetrahydroindol-1-yl, wherein said Het¹ is optionally independently substituted with up to a total of two substituents each independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, hydroxy, benzyl or phenyl; said benzyl and phenyl are each optionally independently substituted with up to three halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfinyl, (C₁-C₆)alkylsulfenyl, trifluoromethyl or hydroxy, or a prodrug thereof or a pharmaceutically acceptable salt of said compound or prodrug.

3 A composition of claim 2 wherein Het¹ is indol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, furano[2,3b]pyridin-2-yl, thieno[2,3b]pyridin-2-yl or imidazo[1,2a]pyridin-4-yl, wherein said Het¹ is optionally independently substituted with up to a total of two substituents independently selected from

fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl and phenyl; said phenyl being optionally substituted with up to two substituents independently selected from fluoro, chloro and (C₁-C₆)alkyl.

4. A composition of claim 1 wherein said first compound is selected
5 from: 6-(3-trifluoromethyl-benzenesulfonyl)-2H-pyridazin-3-one;
6-(4-bromo-2-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(4-trifluoromethyl-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-bromo-benzenesulfonyl)-2H-pyridazin-3-one;
6-(3,4-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
10 6-(4-methoxy-benzenesulfonyl)-2H-pyridazin-3-one;
6-(3-bromo-benzenesulfonyl)-2H-pyridazin-3-one;
6-(biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
6-(4'-fluoro-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
6-(4'-trifluoromethyl-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
15 6-(3',5'-bis-trifluoromethyl-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
6-(biphenyl-2-sulfonyl)-2H-pyridazin-3-one;
6-(4'-trifluoromethyl-biphenyl-2-sulfonyl)-2H-pyridazin-3-one;
6-(2-hydroxy-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
20 6-(3-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,3-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,5-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(4-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
25 6-(2-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,3-difluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,4-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,4-difluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,6-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
30 6-(2-chloro-4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-bromo-4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one; and
6-(naphthalene-1-sulfonyl)-2H-pyridazin-3-one,

or a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

5. A composition of claim 1 wherein said second compound is selected from celecoxib, rofecoxib and etoricoxib or a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

6. A pharmaceutical composition of claim 1 wherein said first 5 compound is in an aldose reductase inhibiting amount.

7. A pharmaceutical composition of claim 1 wherein said second compound is present in a cyclooxygenase-2 inhibiting amount.

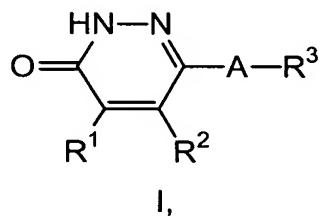
8. A pharmaceutical composition of claim 6 wherein said second compound is present in a cyclooxygenase-2 inhibiting amount.

10 9. A pharmaceutical composition of claim 1 further comprising a vehicle, diluent or carrier.

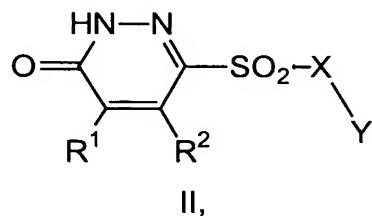
10. A kit comprising:

a first dosage form comprising a first compound selected from:

a compound of formula I



and a compound of formula II



20 or a prodrug of said first compound, or a pharmaceutically acceptable salt of said first compound or said prodrug,

wherein:

A is S, SO or SO₂;

R¹ and R² are each independently hydrogen or methyl;

25 R³ is Het¹, -CHR⁴Het¹ or NR⁶R⁷;

R⁴ is hydrogen or (C₁-C₃)alkyl;

R⁶ is (C₁-C₆)alkyl, aryl or Het²;

R⁷ is Het³;

Het¹ is pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl, cinnolinyl, naphthyridinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyrimidopyridazinyl, pyrimidopyrimidyl, pyridopyrimidyl, pyridopyrazinyl, pyridopyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, pyrrolopyridyl, furopyridyl, thienopyridyl, imidazolopyridyl, oxazolopyridyl, thiazolopyridyl, pyrazolopyridyl, isoxazolopyridyl, isothiazolopyridyl, pyrrolopyrimidyl, furopyrimidyl, thienopyrimidyl, imidazolopyrimidyl, oxazolopyrimidyl, thiazolopyrimidyl, pyrazolopyrimidyl, isoxazolopyrimidyl, isothiazolopyrimidyl, pyrrolopyrazinyl, furopyrazinyl, thienopyrazinyl, imidazolopyrazinyl, oxazolopyrazinyl, thiazolopyrazinyl, pyrazolopyrazinyl, isoxazolopyrazinyl, isothiazolopyrazinyl, pyrrolopyridazinyl, fuopyridazinyl, thienopyridazinyl, imidazolopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, pyrazolopyridazinyl, isoxazolopyridazinyl or isothiazolopyridazinyl; Het¹ is independently optionally substituted with up to a total of four substituents independently selected from R⁸, R⁹, R¹⁰ and R¹¹; wherein R⁸, R⁹, R¹⁰ and R¹¹ are each taken separately and are each independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkyleneoxycarbonyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹²R¹³, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido, phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfenyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to three substituents independently selected from hydroxy,

halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to two substituents independently selected from hydroxy, halo, C₁-C₄)alkyl, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C₁-C₄)alkyl-phenyl optionally substituted in the phenyl portion with one Cl, Br, OMe, Me or SO₂-phenyl wherein said SO₂-phenyl is optionally substituted in the phenyl portion with one Cl, Br, OMe, Me, (C₁-C₄)alkyl optionally substituted with up to five fluoro, or (C₁-C₄)alkoxy optionally substituted with up to three fluoro;

R¹² and R¹³ are each independently hydrogen or (C₁-C₄)alkyl;

Het² and Het³ are each independently imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy; Het² and Het³ are each independently optionally substituted with up to a total of four substituents independently selected from R¹⁴, R¹⁵, R¹⁶ and R¹⁷, wherein R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each taken separately and are each independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylenyloxycarbonyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹⁸R¹⁹, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido, phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro.

substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl,

- 5 (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to three fluoro; and
R¹⁸ and R¹⁹ are each independently hydrogen or (C₁-C₄)alkyl;

X and Y together are CH₂-CH(OH)-Ar or CH₂-C(O)-Ar, or

- 10 X is a covalent bond, NR²⁰ or CHR²¹, wherein, R²⁰ is (C₁-C₃)alkyl or a phenyl that is optionally substituted with one or more substituents selected from OH, F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³, and R²¹ is hydrogen or methyl, and

- 15 Y is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from Ar, OH, F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³;

Ar is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³;

n is independently for each occurrence 0, 1 or 2;

- 20 R²² is independently for each occurrence H, (C₁-C₆)alkyl, phenyl or naphthyl; and

R²³ is independently for each occurrence (C₁-C₆)alkyl, phenyl or naphthyl,

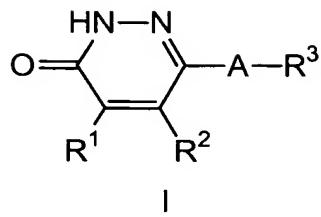
provided that when R³ is NR⁶R⁷, then A is SO₂;

- 25 a second dosage form comprising a second compound that is a cyclooxygenase-2 inhibitor, a prodrug of said second compound or a pharmaceutically acceptable salt of said second compound or said prodrug; and

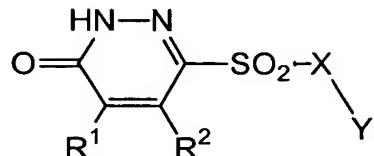
a container.

- 30 11. A therapeutic method comprising administering to a mammal in need of treatment or prevention of diabetic complications a first compound selected from:

a compound of formula I



and a compound of formula II



5

or a prodrug of said first compound, or a pharmaceutically acceptable salt of said first compound or said prodrug,

wherein:

A is S, SO or SO₂;

10 R¹ and R² are each independently hydrogen or methyl;

R³ is Het¹, -CHR⁴Het¹ or NR⁶R⁷;

R⁴ is hydrogen or (C₁-C₃)alkyl;

R⁶ is (C₁-C₆)alkyl, aryl or Het²;

R⁷ is Het³;

15 Het¹ is pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl, cinnolinyl, naphthyridinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyrimidopyridazinyl, pyrimidopyrimidyl, pyridopyrimidyl, pyridopyrazinyl, pyridopyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl,

20 oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, pyrrolopyridyl, furopyridyl, thienopyridyl, imidazolopyridyl, oxazolopyridyl, thiazolopyridyl, pyrazolopyridyl, isoxazolopyridyl, isothiazolopyridyl, pyrrolopyrimidyl, furopyrimidyl, thienopyrimidyl,

25 imidazolopyrimidyl, oxazolopyrimidyl, thiazolopyrimidyl, pyrazolopyrimidyl, isoxazolopyrimidyl, isothiazolopyrimidyl, pyrrolopyrazinyl, furopyrazinyl, thienopyrazinyl, imidazolopyrazinyl, oxazolopyrazinyl, thiazolopyrazinyl, pyrazolopyrazinyl, isoxazolopyrazinyl, isothiazolopyrazinyl, pyrrolopyridazinyl, fuopyridazinyl, thienopyridazinyl, imidazolopyridazinyl, oxazolopyridazinyl,

thiazolopyridazinyl, pyrazolopyridazinyl, isoxazolopyridazinyl or isothiazolopyridazinyl; Het¹ is independently optionally substituted with up to a total of four substituents independently selected from R⁸, R⁹, R¹⁰ and R¹¹; wherein R⁸, R⁹, R¹⁰ and R¹¹ are each taken separately and are each independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylenyloxycarbonyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹²R¹³, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido, phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfenyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to two substituents independently selected from hydroxy, halo, C₁-C₄)alkyl, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C₁-C₄)alkyl-phenyl optionally substituted in the phenyl portion with one Cl, Br, OMe, Me or SO₂-phenyl wherein said SO₂-phenyl is optionally substituted in the phenyl portion with one Cl, Br, OMe, Me, (C₁-C₄)alkyl optionally substituted with up to five fluoro, or (C₁-C₄)alkoxy optionally substituted with up to three fluoro;

R¹² and R¹³ are each independently hydrogen or (C₁-C₄)alkyl;

Het² and Het³ are each independently imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy,

thiophenoxy; Het² and Het³ are each independently optionally substituted with up to a total of four substituents independently selected from R¹⁴, R¹⁵, R¹⁶ and R¹⁷, wherein R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each taken separately and are each independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkyleneoxycarbonyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹⁸R¹⁹, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido, phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfenyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to three fluoro; and R¹⁸ and R¹⁹ are each independently hydrogen or (C₁-C₄)alkyl;

X and Y together are CH₂-CH(OH)-Ar or CH₂-C(O)-Ar, or

X is a covalent bond, NR²⁰ or CHR²¹, wherein, R²⁰ is (C₁-C₃)alkyl or a phenyl that is optionally substituted with one or more substituents selected from OH, F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³, and R²¹ is hydrogen or methyl, and

Y is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from Ar, OH, F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³,

Ar is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂—NR²²R²³;

n is independently for each occurrence 0, 1 or 2;

5 R²² is independently for each occurrence H, (C₁-C₆)alkyl, phenyl or naphthyl; and

R²³ is independently for each occurrence (C₁-C₆)alkyl, phenyl or naphthyl,

provided that when R³ is NR⁶R⁷, then A is SO₂,

10 and a second compound that is a cyclooxygenase-2 inhibitor, a prodrug of said second compound or a pharmaceutically acceptable salt of said second compound or said prodrug.

12. A therapeutic method of claim 11 wherein said first compound is a compound of formula I, wherein A is SO₂; R¹ and R² are each hydrogen; R³ is Het¹, wherein Het¹ is 5H-furo-[3,2c]pyridin-4-one-2-yl, furano[2,3b]pyridin-2-yl, thieno[2,3b]pyridin-2-yl, indol-2-yl, indol-3-yl, benzofuran-2-yl, benzothien-2-yl, imidazo[1,2a]pyridin-3-yl, pyrrol-1-yl, imidazol-1-yl, indazol-1-yl, tetrahydroquinol-1-yl or tetrahydroindol-1-yl, wherein said Het¹ is optionally independently substituted with up to a total of two substituents each independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, hydroxy, benzyl or phenyl; said benzyl and phenyl are each optionally independently substituted with up to three halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfinyl, (C₁-C₆)alkylsulfenyl, trifluoromethyl or hydroxy, or a prodrug thereof or a pharmaceutically acceptable salt of said compound or prodrug.

13. A therapeutic method of claim 12 wherein Het¹ is indol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, furano[2,3b]pyridin-2-yl, thieno[2,3b]pyridin-2-yl or imidazo[1,2a]pyridin-4-yl, wherein said Het¹ is optionally independently substituted with up to a total of two substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl and phenyl; said phenyl being optionally substituted with up to two substituents independently selected from fluoro, chloro and (C₁-C₆)alkyl.

14. A therapeutic method of claim 11 wherein said first compound is selected from: 6-(3-trifluoromethyl-benzenesulfonyl)-2H-pyridazin-3-one;

- 6-(4-bromo-2-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(4-trifluoromethyl-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-bromo-benzenesulfonyl)-2H-pyridazin-3-one;
6-(3,4-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
- 5 6-(4-methoxy-benzenesulfonyl)-2H-pyridazin-3-one;
6-(3-bromo-benzenesulfonyl)-2H-pyridazin-3-one;
6-(biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
6-(4'-fluoro-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
6-(4'-trifluoromethyl-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
- 10 6-(3',5'-bis-trifluoromethyl-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
6-(biphenyl-2-sulfonyl)-2H-pyridazin-3-one;
6-(4'-trifluoromethyl-biphenyl-2-sulfonyl)-2H-pyridazin-3-one;
6-(2-hydroxy-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
- 15 6-(3-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,3-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,5-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(4-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
- 20 6-(2-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,3-difluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,4-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,4-difluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,6-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
- 25 6-(2-chloro-4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-bromo-4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one; and
6-(naphthalene-1-sulfonyl)-2H-pyridazin-3-one,
or a prodrug thereof or a pharmaceutically acceptable salt of said compound
or said prodrug.
- 30 15. A therapeutic method of claim 11 wherein said second
compound is selected from celecoxib, rofecoxib and etoricoxib or a prodrug
thereof or a pharmaceutically acceptable salt of said compound or said
prodrug.

16. A therapeutic method of claim 11 wherein said first compound is administered in an aldose reductase inhibiting amount.

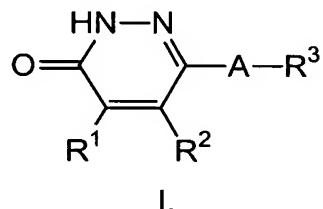
17. A therapeutic method of claim 11 wherein said second compound is administered in a cyclooxygenase-2 inhibiting amount.

5 18. A therapeutic method of claim 16 wherein said second compound is administered in a cyclooxygenase-2 inhibiting amount.

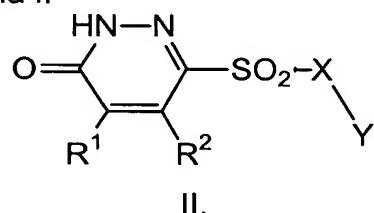
19. A therapeutic method of claim 11 wherein said mammal is a human.

10 20. A therapeutic method comprising administering to a mammal in need of treatment or prevention of cardiac tissue ischemia a first compound selected from:

a compound of formula I



15 and a compound of formula II



or a prodrug of said first compound, or a pharmaceutically acceptable salt of said first compound or said prodrug,

20 wherein:

A is S, SO or SO₂;

R¹ and R² are each independently hydrogen or methyl;

R³ is Het¹, -CHR⁴Het¹ or NR⁶R⁷;

R⁴ is hydrogen or (C₁-C₃)alkyl;

25 R⁶ is (C₁-C₆)alkyl, aryl or Het²;

R⁷ is Het³;

Het¹ is pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl, cinnolinyl, naphthyridinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyrimidopyridazinyl, pyrimidopyrimidyl,

pyridopyrimidyl, pyridopyrazinyl, pyridopyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzisoxazolyl,
 5 benzisothiazolyl, pyrrolopyridyl, furopyridyl, thienopyridyl, imidazolopyridyl, oxazolopyridyl, thiazolopyridyl, pyrazolopyridyl, isoxazolopyridyl, isothiazolopyridyl, pyrrolopyrimidyl, furopyrimidyl, thienopyrimidyl, imidazolopyrimidyl, oxazolopyrimidyl, thiazolopyrimidyl, pyrazolopyrimidyl, isoxazolopyrimidyl, isothiazolopyrimidyl, pyrrolopyrazinyl, fuopyrazinyl,
 10 thienopyrazinyl, imidazolopyrazinyl, oxazolopyrazinyl, thiazolopyrazinyl, pyrazolopyrazinyl, isoxazolopyrazinyl, isothiazolopyrazinyl, pyrrolopyridazinyl, fuopyridazinyl, thienopyridazinyl, imidazolopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, pyrazolopyridazinyl, isoxazolopyridazinyl or isothiazolopyridazinyl; Het¹ is independently optionally substituted with up to a
 15 total of four substituents independently selected from R⁸, R⁹, R¹⁰ and R¹¹; wherein R⁸, R⁹, R¹⁰ and R¹¹ are each taken separately and are each independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylenyloxycarbonyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹²R¹³, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido,
 20 phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfenyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy
 25 optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in

the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to two substituents independently selected from hydroxy, halo, C₁-C₄)alkyl, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C₁-C₄)alkyl-phenyl optionally substituted in the phenyl portion with one Cl, Br, OMe, Me or SO₂-phenyl

5 wherein said SO₂-phenyl is optionally substituted in the phenyl portion with one Cl, Br, OMe, Me, (C₁-C₄)alkyl optionally substituted with up to five fluoro, or (C₁-C₄)alkoxy optionally substituted with up to three fluoro;

R¹² and R¹³ are each independently hydrogen or (C₁-C₄)alkyl;

Het² and Het³ are each independently imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy; Het² and Het³ are each independently optionally substituted with up to a total of four substituents independently selected from R¹⁴, R¹⁵, R¹⁶ and

15 R¹⁷, wherein R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each taken separately and are each independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylenyloxycarbonyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹⁸R¹⁹, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido,

phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfenyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy

25 optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are optionally substituted with up to three substituents independently selected from hydroxy,

halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are optionally substituted with up to two

substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to three fluoro; and R¹⁸ and R¹⁹ are each independently hydrogen or (C₁-C₄)alkyl;

- 5 X and Y together are CH₂-CH(OH)-Ar or CH₂-C(O)-Ar, or
X is a covalent bond, NR²⁰ or CHR²¹, wherein, R²⁰ is (C₁-C₃)alkyl or a phenyl that is optionally substituted with one or more substituents selected from OH, F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³, and R²¹ is hydrogen or methyl, and
- 10 Y is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from Ar, OH, F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³;
Ar is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl,
- 15 S(O)_n-(C₁-C₆)alkyl and SO₂-NR²²R²³;
n is independently for each occurrence 0, 1 or 2;
- 20 R²² is independently for each occurrence H, (C₁-C₆)alkyl, phenyl or naphthyl; and
R²³ is independently for each occurrence (C₁-C₆)alkyl, phenyl or naphthyl,
provided that when R³ is NR⁶R⁷, then A is SO₂,
and a second compound that is a cyclooxygenase-2 inhibitor, a prodrug of said second compound or a pharmaceutically acceptable salt of said second compound or said prodrug.
- 25 21. A therapeutic method of claim 20 wherein said first compound is a compound of formula I, wherein A is SO₂; R¹ and R² are each hydrogen; R³ is Het¹, wherein Het¹ is 5H-furo-[3,2c]pyridin-4-one-2-yl, furano[2,3b]pyridin-2-yl, thieno[2,3b]pyridin-2-yl, indol-2-yl, indol-3-yl, benzofuran-2-yl, benzothien-2-yl, imidazo[1,2a]pyridin-3-yl, pyrrol-1-yl, imidazol-1-yl, indazol-1-yl,
- 30 tetrahydroquinol-1-yl or tetrahydroindol-1-yl, wherein said Het¹ is optionally independently substituted with up to a total of two substituents each independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, hydroxy, benzyl or phenyl; said benzyl and phenyl are each optionally independently substituted with up to three halo, (C₁-C₆)alkyl, (C₁-

C_6)alkoxy, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfenyl, trifluoromethyl or hydroxy, or a prodrug thereof or a pharmaceutically acceptable salt of said compound or prodrug.

22. A therapeutic method of claim 21 wherein Het¹ is indol-2-yl,
 5 benzofuran-2-yl, benzothiophen-2-yl, furano[2,3b]pyridin-2-yl, thieno[2,3b]pyridin-2-yl or imidazo[1,2a]pyridin-4-yl, wherein said Het¹ is optionally independently substituted with up to a total of two substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, trifluoromethyl and phenyl; said phenyl being optionally substituted with up to
 10 two substituents independently selected from fluoro, chloro and (C_1-C_6)alkyl.

23. A therapeutic method of claim 20 wherein said first compound is selected from: 6-(3-trifluoromethyl-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(4-bromo-2-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(4-trifluoromethyl-benzenesulfonyl)-2H-pyridazin-3-one;
 15 6-(2-bromo-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(3,4-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(4-methoxy-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(3-bromo-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
 20 6-(4'-fluoro-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
 6-(4'-trifluoromethyl-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
 6-(3',5'-bis-trifluoromethyl-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;
 6-(biphenyl-2-sulfonyl)-2H-pyridazin-3-one;
 25 6-(4'-trifluoromethyl-biphenyl-2-sulfonyl)-2H-pyridazin-3-one;
 6-(2-hydroxy-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(2-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(3-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
 30 6-(2,3-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(2,5-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(4-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(2-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(2,3-difluoro-benzenesulfonyl)-2H-pyridazin-3-one;
 6-(2,4-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(2,4-difluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,6-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-chloro-4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-bromo-4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one; and
5 6-(naphthalene-1-sulfonyl)-2H-pyridazin-3-one,

or a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

24. A therapeutic method of claim 20 wherein said second compound is selected from celecoxib, rofecoxib and etoricoxib or a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.
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25. A therapeutic method of claim 20 wherein said first compound is administered in an aldose reductase inhibiting amount.

26. A therapeutic method of claim 20 wherein said second compound is administered in a cyclooxygenase-2 inhibiting amount.
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27. A therapeutic method of claim 25 wherein said second compound is administered in a cyclooxygenase-2 inhibiting amount.

28. A therapeutic method of claim 20 wherein said mammal is a human.
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